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(71) Applicant *(for all designated States except US)*: BOKWANG CO., LTD. [KR/KR]; Glass Tower Building, 30F, 946–1 Daichi–dong, Kangnam–ku, Seoul 135–280 (KR).

(71)(72) Applicant and Inventor: LEE, Kyu–Ho [KR/KR]; 7–201 Hyundai Villa, 172 Sangil–dong, Kandong–ku, Seoul 134–090 (KR).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: KIM, Kyung–Chae [KR/KR]; 130 Kongdan–dong, Kumi–shi, Kyungsang-buk–do 730–030 (KR).

(74) Agent: LEE, Kuiy, Dong; Seoul Building, 114–31, Uni–dong, Chongro–ku, Seoul 110–350 (KR).

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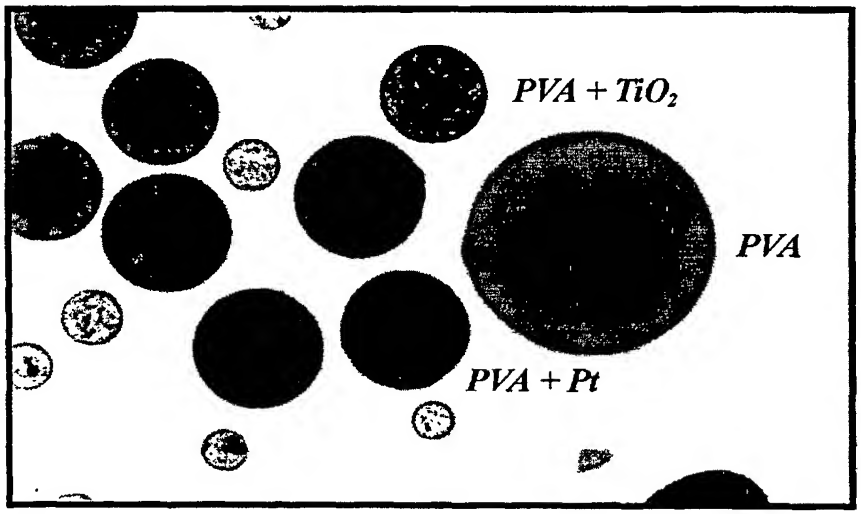
(54) Title: VASCULAR EMBOLIC MATERIALS HAVING MULTIFUNCTIONS



Bead form

(57) Abstract

The present invention relates to a vascular embolic material for use in the treatment of an angiotropy of various tumors and a vascular malformation. Specifically, the present invention relates to a vascular embolic material having the specific morphological, physicochemical and radiological characteristics and multifunction in the form of a bead or a sponge comprising a mixture of a hydrophilic polymer material and a metal material. The specific physicochemical and radiological characteristics of the vascular embolic material according to the present invention facilitate its clinical use and aid in the diagnosis before and after the embolization. Further, a local radiation treatment and anticancer treatment is possible and thus the therapeutic effect on said disorders can be enhanced.

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VASCULAR EMBOLIC MATERIALS HAVING MULTIFUNCTIONS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a vascular embolic material for use in the treatment of an angiotropy of various tumors and a vascular malformation. Specifically, the present invention relates to a vascular embolic material having the specific morphological, physicochemical and radiological characteristics and multifunction in the form of a bead or a sponge comprising a mixture of a hydrophilic polymer material and a metal material.

2. Description of the Prior Art

Various vascular embolic materials are generally used to block an angiotropy or vascular malformation by infusing them via a fine vascular catheter while subjecting to angiography.

Various kinds of materials that are harmless to the human body and that which do not bring about adverse reactions are selected and used as a vascular embolic material depending on the purposes. However, it is now required in clinical therapeutics for the materials to have the deliverability of a specific drug, a radioactive isotope, etc., to a local region as the capability to block blood vessels.

SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide a new vascular embolic material having multifunction in the form of a bead or a sponge, which is harmless to the human body, hydrophilic and substantially permanent and moreover has the specific morphological, physicochemical and radiological characteristics and the deliverability of a specific drug and a radioactive isotope.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1a and 1b are drawings showing polyvinyl alcohol materials in the form of a bead and a sponge, respectively.

Figures 2a and 2b are drawings showing the new vascular embolic materials in the form of a bead or a sponge, respectively.

Figure 3 is a drawing showing the result from a vascular embolization of a kidney of a rabbit.

Figure 4 is an X-ray photographic image of a mixture of polyvinyl alcohol and TiO_2.

Figure 5 is a CT photographic image of a mixture of polyvinyl alcohol and TiO_2.

Figure 6 is an MRI photographic image of a mixture of polyvinyl alcohol and TiO_2.

DETAILED DESCRIPTION OF THE INVENTION

The object of the present invention is established by a vascular embolic material having multifunction in the form of a bead or a sponge comprising a mixture of a hydrophilic polymer material and a metal material.

Therefore, the present invention is directed to a vascular embolic material having multifunction in the form of a bead or a sponge comprising a mixture of a hydrophilic polymer material and a metal material.

According to the present invention, polyvinyl alcohol is primarily used as the polymer material constituting the vascular embolic material. Polyvinyl alcohol

having a molecular weight of 50,000 to 300,000 is preferably used. The metal material is preferred from the group consisting of TiO_2, Pt or a mixture of TiO_2 and Pt. The mixing ratio of the polymer material and the metal material should preferably be 4-10:1.

The characteristics of the vascular embolic material according to the present invention will be described in greater detail in the following section.

Morphological characteristics

The vascular embolic material according to the present invention has either a bead or a sponge form, as shown in Figures 2a and 2b. Such vascular embolic material may be prepared in various sizes of 10 to 1000 μm and easily infused into a very fine vascular catheter.

The result from a vascular embolization of a kidney of a rabbit (a pre-animal test) is shown in Figure 3.

Physicochemical characteristics

The vascular embolic material according to the present invention is prepared using polyvinyl alcohol, with a molecular weight of 50,000 to 300,000, as a polymer material and TiO_2 (99.95% of purity), Pt (99.9999% of purity) or a mixture of TiO_2 and Pt having a size of 0.02 to 2 μm. Such vascular embolic material has a specific gravity of 1.2 to 2.5, has a strong hydrophilicity and is harmless to the human body.

Radiological characteristics

Most vascular embolic materials currently used cannot be clearly recognized after the embolization since they appear transparent to radiation (X-ray).

However, the vascular embolic material according to the present invention includes a metal material that is visible to X-ray and thus the position can be seen. Therefore, the vascular embolic material according to the present invention shows an opaque image in an X-ray photography (see Figure 4).

Also, the vascular embolic material according to the present invention shows a high-density image in a computerized tomography (see Figure 5). Further, such vascular embolic material does not affect an image during a magnetic resonance imaging and shows a low resonance image (see Figure 6).

Multifunctionality

An irradiation and an anticancer agent are generally used to treat a tumor. In order to enhance the therapeutic effect and reduce the possibility of an adverse reaction to the whole body, an irradiation of a radiation or infusion of an anticancer agent on a local legion is carried out in clinical therapeutics.

The vascular embolic material according to the present invention has an embolization effect of blocking an angiotropy. Further, such vascular embolic material may itself become isotoped by isotoping a metal material and thus having the deliverability of β-ray and γ-ray useful for the treatment. In addition, it is possible to add a drug such as an anticancer agent to the vascular embolic material to enhance the therapeutic effect on a local legion.

The vascular embolic material according to the present invention may be prepared by a method for drying in oil or a freeze drying method.

PREFERRED EMBODIMENT OF THE INVENTION

The present invention will be described in greater detail by way of the following examples, which are not intended to limit the invention.

Example 1

Preparation of the vascular embolic material in the form of a bead by a method for drying in oil

7 % by weight of polyvinyl alcohol and 0.5 to 1.75 % by weight of Pt or TiO_2 powder were placed on a tertiary distilled water in a beaker while stirring at 700 rpm for 30 minutes. The solution was gradually heated from 30 °C to 80 °C while stirring for 2 to 3 hours and increasing the stirring speed to 1000 rpm in order to completely dissolve polyvinyl alcohol. Then, the solution was sealed and left for 12 hours or so at room temperature to remove the bubbles therein.

0.3 % by weight of sorbitan monostearate as a surfactant was added to 1 kg dispersion of liquid paraffin and gradually heated from room temperature to 70 °C and stirred at 1200 rpm. The mixed solution of polyvinyl alcohol and a metal material (Pt or TiO_2) was infused into the stirred liquid by a syringe to make it a fine drop state. The dispersion was heated in a bath at 95 °C to 110 °C for 4 hours to gradually dry the drop and to prepare a mixture of polyvinyl alcohol and a metal in the form of a bead. The mixture was filtered out while maintaining the temperature of 60 ± 5 °C, repeatedly washing with n-hexane and drying under the reduced pressure. The dried materials were classified by size through a sieve.

Polyvinyl alcohol and a metal material were mixed so as that the ratio of the solid components is 4:1. When two kinds of metal materials were used together, the ratio between the two was varied depending on the purposes but the total amount between polyvinyl alcohol and a metal material was kept the same. Even the vascular embolic material in the form of a bead was prepared with polyvinyl alcohol only, the amount of polyvinyl alcohol was 8 % by weight and an anticancer agent was further added at an adequate amount.

Example 2

Preparation of the vascular embolic material in the form of a sponge by a freeze drying method

A mixed solution of polyvinyl alcohol and a metal material was prepared by the same method, as described in example 1. An equivalent amount of ammonium bicarbonate [$(NH_4)_2CO_3$] was added to the solution at room temperature so as that the ratio of the solid components is 1:1, and was mixed well. The bubbles formed at room temperature in vacuum state (10^3 torr). The vessel was frozen by quenching with liquid nitrogen to -170 °C and this state was maintained for 10 minutes. It was confirmed that the materials in the vessel were completely frozen. Liquid nitrogen was removed and then moisture was further removed in vacuum state for 30 minutes. Thereafter, additionally moisture was removed by dipping into a mixed solution of an ice water and salt in vacuum state at -10 °C for 1 hour. After drying at room temperature in vacuum state for 4 hours, the resultant was dried again in a water bath at 50 °C for 1 hour to completely remove moisture. Finally, liquid nitrogen was placed in the vessel and the materials in the vessel were pulverized and classified by size through a sieve.

Even when only polyvinyl alcohol was used without adding a metal material, the component ratio to ammonium bicarbonate was maintained in 1:1. An anticancer agent was further added in an adequate amount.

Example 3

Isotoping of the vascular embolic material according to the present invention

A metal material included in the vascular embolic material according to the present invention was irradiated in the core of a nuclear reaction (Hanaro) and a region where neutrons were generated in 1.7×10^{13} /cm^2/sec for 1 minute and 10 minutes. β-ray and γ-ray emitted from the material was determined by a neutron activation analysis using Multi-Channel Detector and thus isotoping was confirmed.

The results are shown in Table 1.

Table 1

Polyvinyl alcohol + TiO_2 + Pt(2), after (n, gamma) reaction, NAA

Elements	Concentration	Radioneuclides	β-ray	γ-ray
Ti	11.60%	Ti-51	1.56 MeV (8%)	0.32 MeV (93%)
			2.17 MeV (92%)	0.61 MeV (1.2%)
				0.93 MeV (4.9%)
Pt	3.13	Pt-199	in-progress	
Na	0.56	Na-24	in-progress	
Cl	563 ppm	Cl-38	in-progress	
Al	130	Al-28	in-progress	
V	1.5	V-52	in-progress	

Example 4

Anticancer effect of the vascular embolic material according to the present invention

5 to 50 mg of cisplastin among anticancer agents was added to the vascular embolic material according to the present invention and applied to a cultured cancerous cell. Then the anticancer effect was determined.

The results using 23.98 mg of cisplatin (NAA) are set forth in Table 2.

Table 2

Elements	Radioisotope	$T_{1/2}$	Concentration
Pt	Pt-195m	96.48 hr	6.22±0.06 %
Au	Au-198	64.80	6.42±0.02 ppm
Na	Na-24	15.0	2.67±0.15 %
Cl	Cl-38	37.7 min	3.69±0.02 %

According to the present invention, a vascular embolic material for use in the treatment of a tumor and a vascular malformation is provided. The specific physicochemical and radiological characteristics of the material according to the present invention facilitate its clinical use and aid in the diagnosis before and after the embolization. Further, a local radiation treatment and anticancer treatment is possible and thus the therapeutic effect on said disorders can be enhanced.

What Is Claimed Is:

1. A vascular embolic material having multifunction in the form of a bead or a sponge comprising a mixture of a hydrophilic polymer material and a metal material.

2. The vascular embolic material according to Claim 1, wherein the hydrophilic polymer material is polyvinyl alcohol having a molecular weight of 50,000 to 300,000.

3. The vascular embolic material according to Claim 1, wherein the metal material is selected from the group consisting of TiO_2, Pt or a mixture of TiO_2 and Pt.

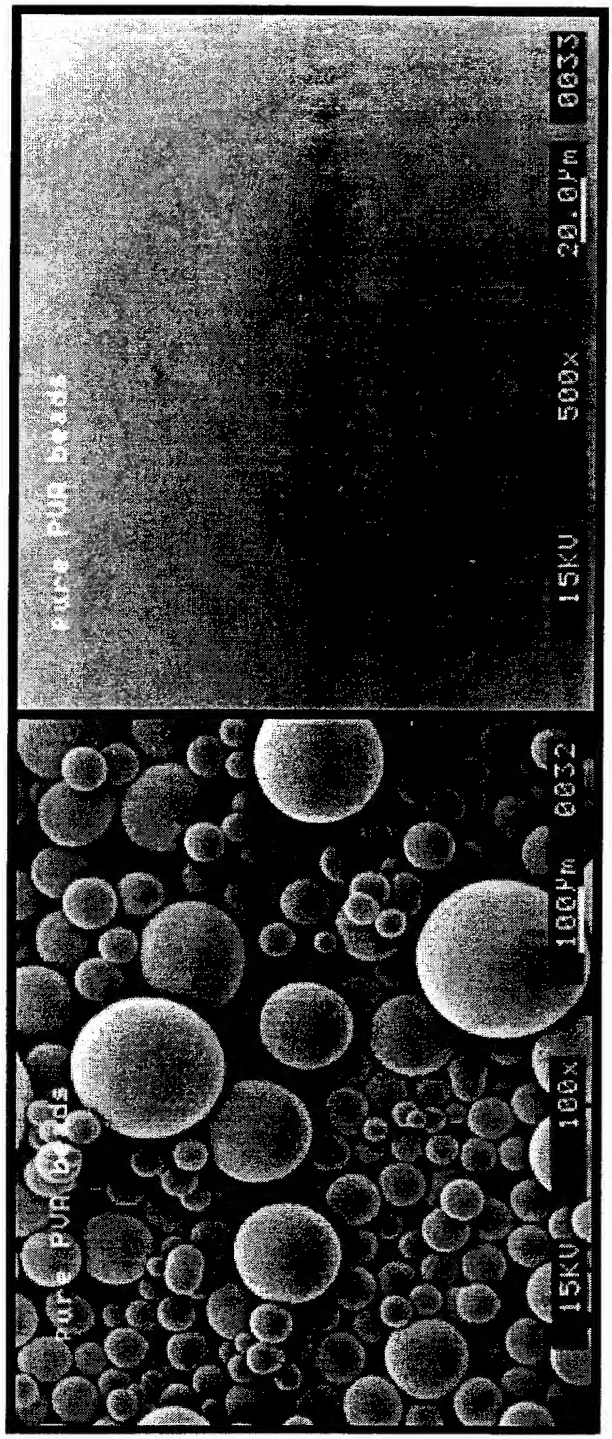
4. The vascular embolic material according to Claim 1, wherein the mixing ratio of the hydrophilic polymer material and the metal material is 4-10:1.

5. The vascular embolic material according to Claim 1, which is isotoped by a neutron radiation.

6. The vascular embolic material according to Claim 1 further comprising a drug.

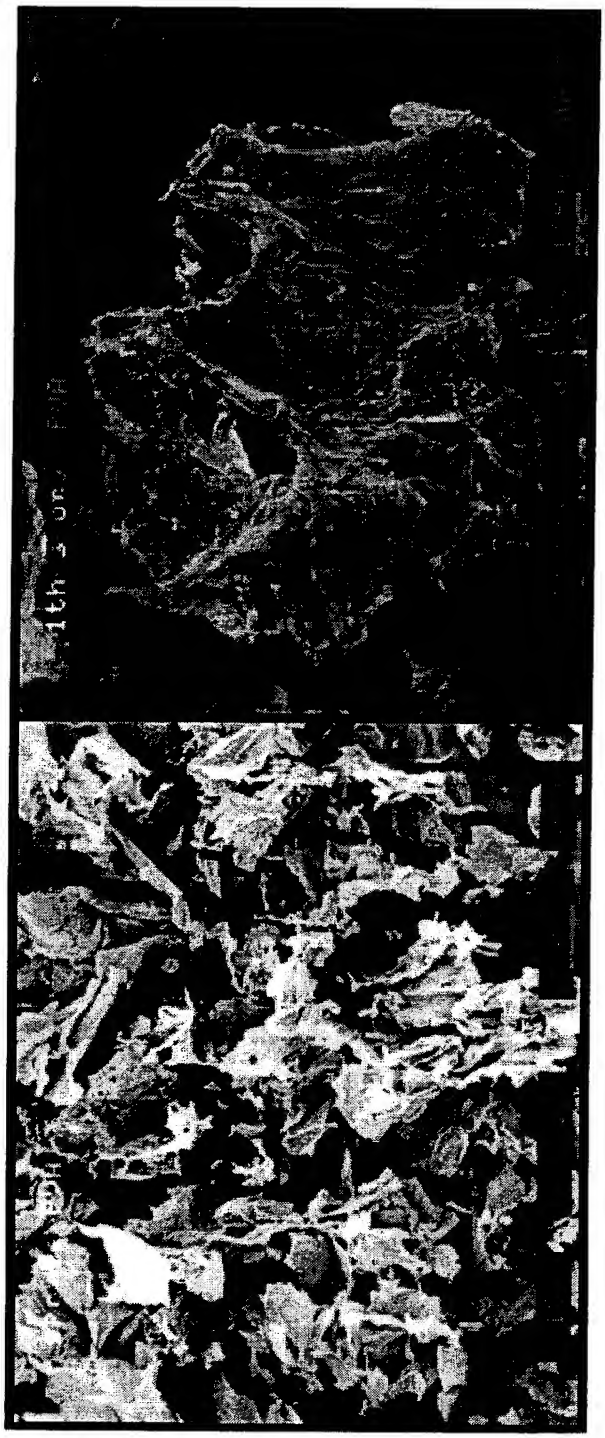
7. The vascular embolic material according to Claim 6, wherein the drug is an anticancer agent.

Fig. 1a



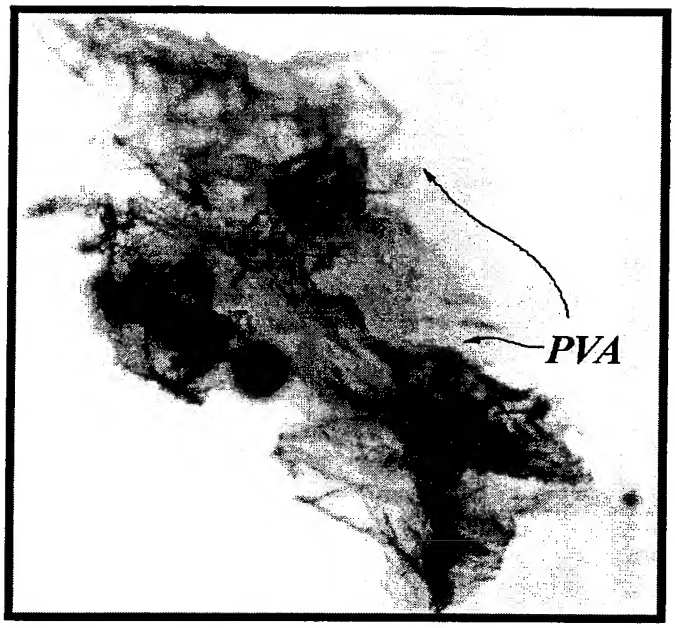
SEM *surface*

Fig. 1b



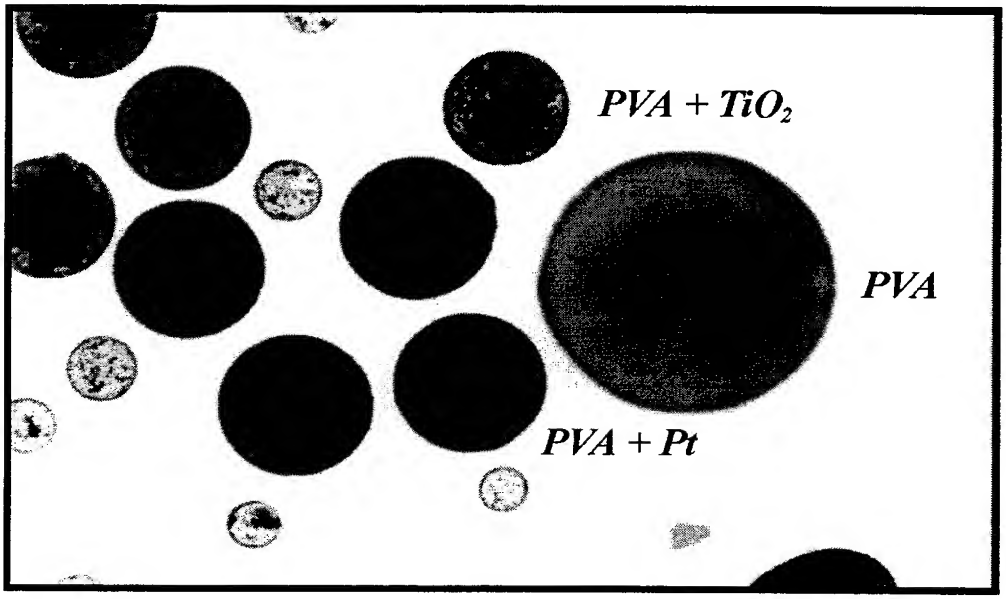
SEM

Fig. 2a



Sponge form

Fig. 2b



Bead form

Fig. 3

PVA,100 X LM

Fig. 4

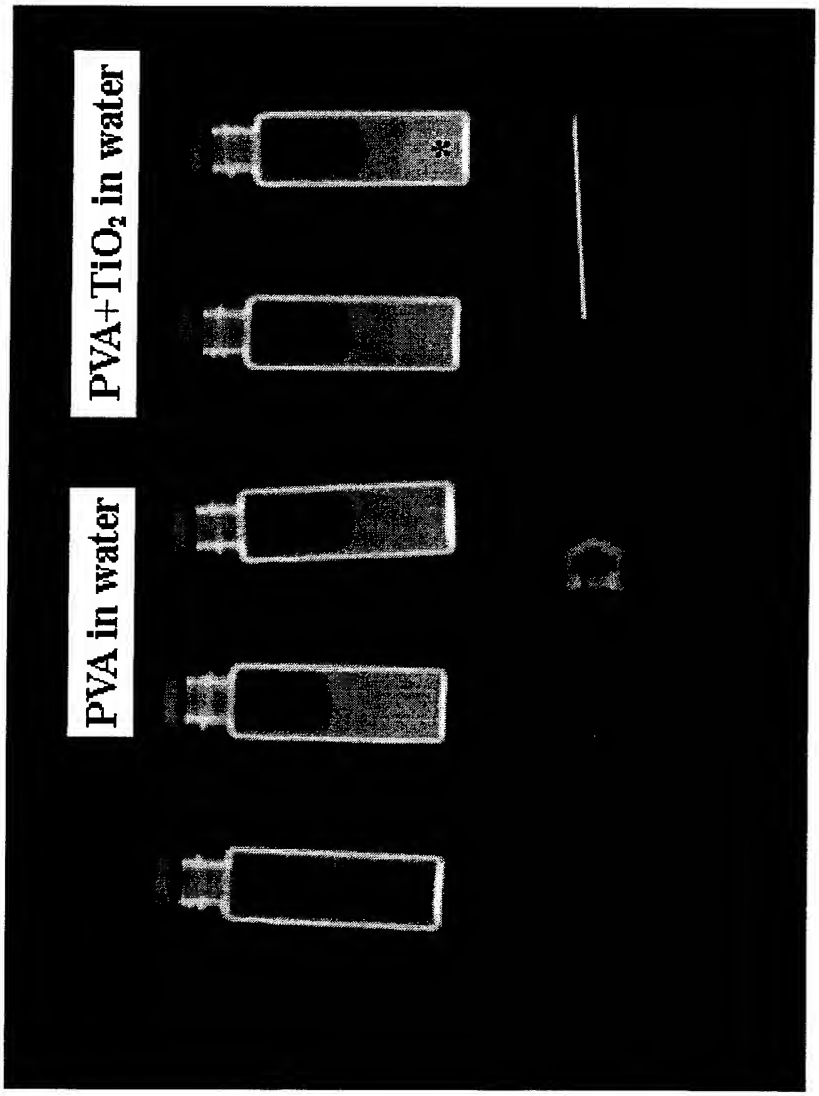


Fig. 5

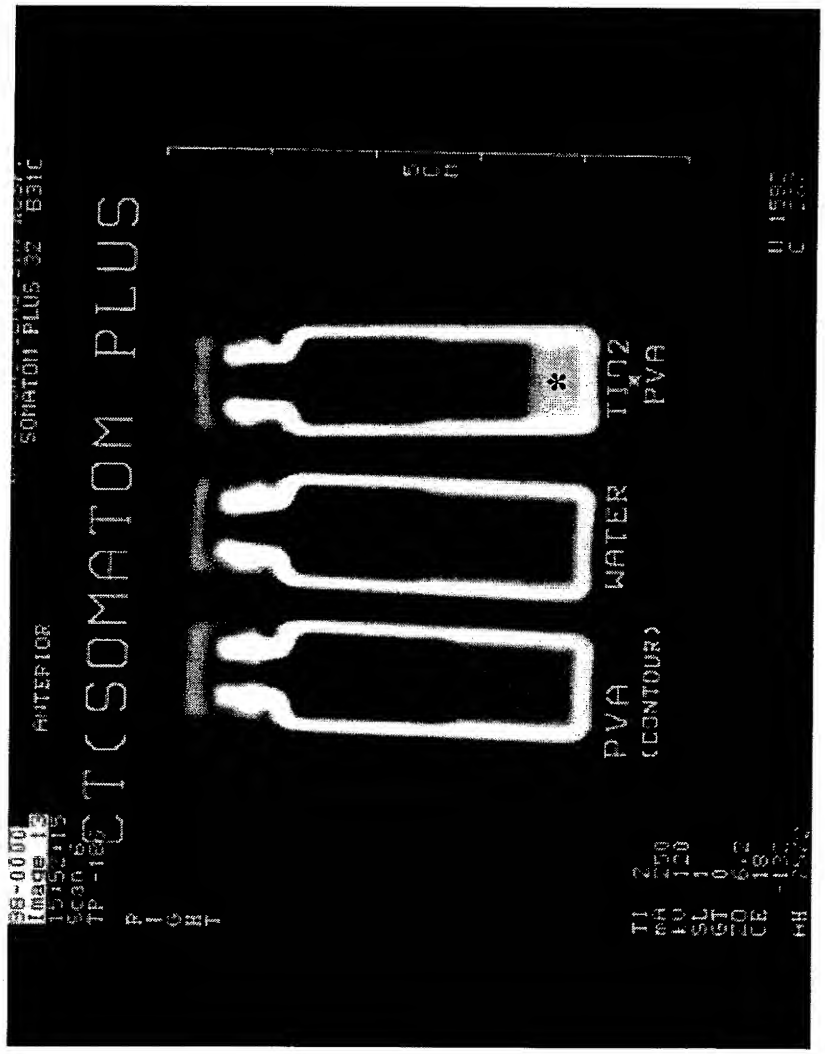
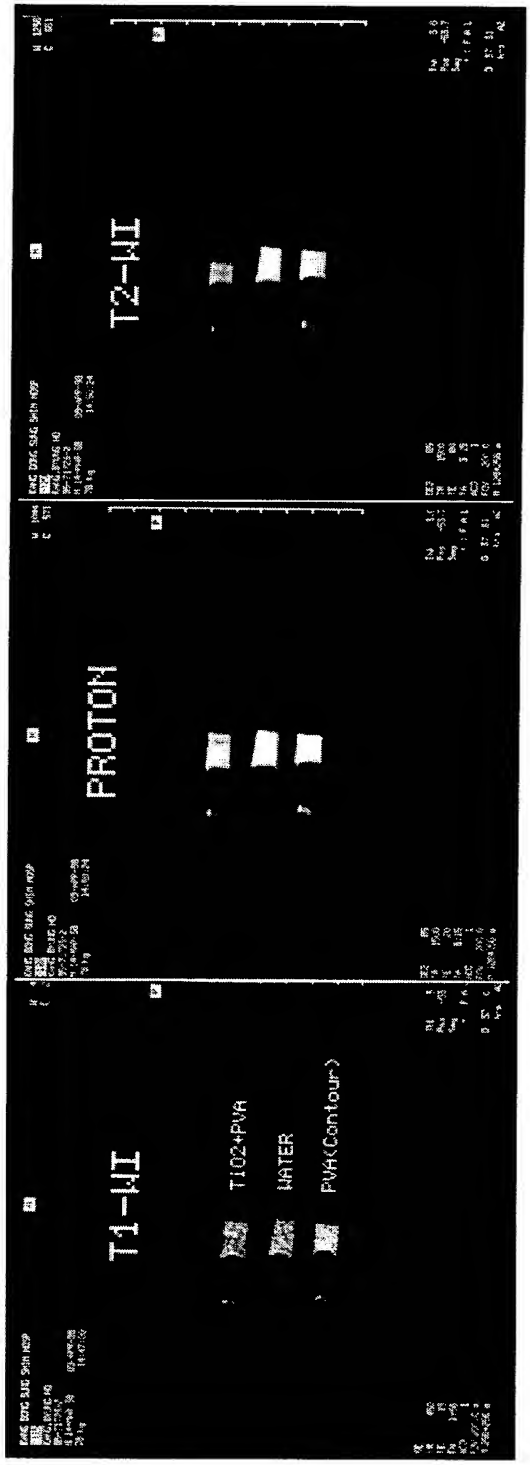


Fig. 6



INTERNATIONAL SEARCH REPORT

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CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A 61 K 51/12, 49/00, 32/24, 47/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/12577 A1 (NYCOMED IMAGING AS) 18 March 1999 (18.03.99) abstract; page 5, line 14 - page 11, line 2; page 16, lines 1-8; claims.	1,2,5-7
X	JP 5000969 A (TAKEDA CHEM IND LTD) 8 January 1993 (08.01.93) (abstract) PAJ (online). London, U.K.: Derwent Pub. Ltd. Retrieved from EPOQUE, ABV-017251, ABD-1993	1,6,7
X	JP 6329542 A (KIBUN FOOD CHEMIPHAR KK) 29 November 1994 (29.11.94) (abstract) World Patent Index (online). London, U.K.: Derwent Pub. Ltd. Retrieved from EPOQUE, DW 199507 Acc.No.1995-048756.	1,6,7
X	US 5886026 A (WILLIAM L. et al.) 23 March 1999 (23.03.99) abstract; column 3, line 65 - column 4, line 16.	1,3,6,7
P,X	US 6015541 A (GREFF R.J.) 18 January 2000 (18.01.00) abstract; claims. ----	1,3,5-7

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Patent document cited in search report			Publication date	Patent family member(s)			Publication date
WO	A1	9912577	18-03-1999	AU	A1	88770/98	29-03-1999
JP	A2	5000969	08-01-1993	AT	E	130517	15-12-1995
				CA	AA	2048544	09-02-1992
				DE	C0	69114782	04-01-1996
				DE	T2	69114782	18-04-1996
				EP	A1	470569	12-02-1992
				EP	B1	470569	22-11-1995
				US	A	5202352	13-04-1993
JP	A2	6329542	29-11-1994			none	
US	A	5886026	23-03-1999	AT	E	154757	15-07-1997
				AU	A1	71192/94	20-02-1995
				AU	B2	693797	09-07-1998
				AU	A1	69911/98	16-07-1998
				CA	AA	2167268	02-02-1995
				CN	A	1130866	11-09-1996
				DE	C0	69403966	31-07-1997
				DE	T2	69403966	05-02-1998
				DK	T3	706376	13-10-1997
				EP	A1	706376	17-04-1996
				EP	B1	706376	25-06-1997
				EP	A2	797988	01-10-1997
				ES	T3	2106553	01-11-1997
				GR	T3	3024833	30-01-1998
				JP	T2	9503488	08-04-1997
				NO	A0	960226	18-01-1996
				NO	A	960226	18-03-1996
				NZ	A	268326	19-12-1997
				WO	A1	9503036	02-02-1995
				US	A	5716981	10-02-1998
				US	A	5994341	30-11-1999
US	A	6015541	18-01-2000	AU	A1	12705/99	24-05-1999
				AU	A1	13784/99	24-05-1999
				WO	A1	9922774	14-05-1999
				WO	A1	9922775	14-05-1999

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(71) Applicant *(for all designated States except US)*: **PHOENIX DISPLAY ELECTRONICS CO., LTD.** [KR/KR]; 130 Kongdan-dong, Kumi-shi, Kyungsang-buk-do 730-030 (KR).

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(74) Agent: **LEE, Kuiy, Dong**; Seoul Building, 114-31, Uni-dong, Chongro-ku, Seoul 110-350 (KR).

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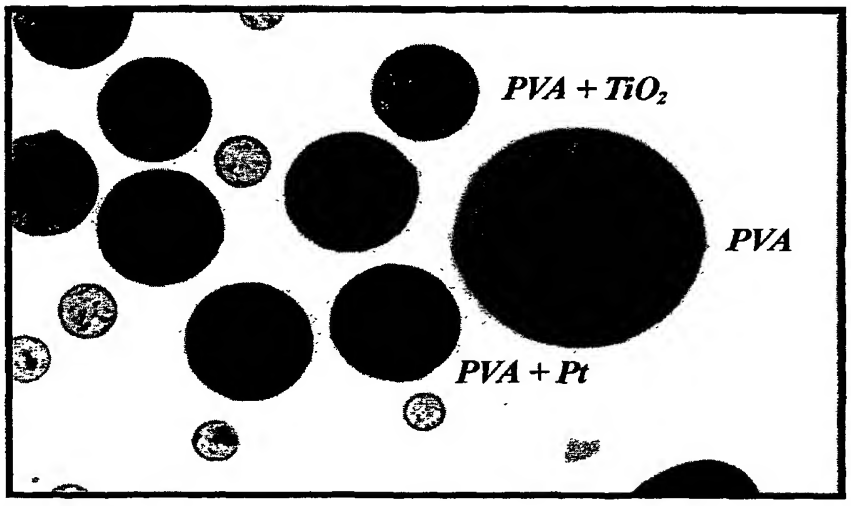

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X	WO 99/12577 A1 (NYCOMED IMAGING AS) 18 March 1999 (18.03.99) abstract; page 5, line 14 - page 11, line 2; page 16, lines 1-8; claims.	1,2,5-7
X	JP 5000969 A (TAKEDA CHEM IND LTD) 8 January 1993 (08.01.93) (abstract) PAJ (online). London, U.K.: Derwent Pub. Ltd. Retrieved from EPOQUE, ABV-017251, ABD-1993	1,6,7
X	JP 6329542 A (KIBUN FOOD CHEMIPHAR KK) 29 November 1994 (29.11.94) (abstract) World Patent Index (online). London, U.K.: Derwent Pub. Ltd. Retrieved from EPOQUE, DW 19	1,6,7
X	US 5886026 A (WILLIAM L. et al.) 23 March 1999 (23.03.99) abstract; column 3, line 65 - column 4, line 16.	1,3,6,7
P,X	US 6015541 A (GREFF R.J.) 18 January 2000 (18.01.00) abstract; claims.	1,3,5-7

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
13 July 2000 (13.07.2000)	7 August 2000 (07.08.2000)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Krenn Telephone No. 1/53424/435

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AMENDED SHEET

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 00/00420

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
WO	A1	9912577	18-03-1999	AU	A1	88770/98	29-03-1999
JP	A2	5000969	08-01-1993	AT	E	130517	15-12-1995
				CA	AA	2048544	09-02-1992
				DE	C0	69114782	04-01-1996
				DE	T2	69114782	18-04-1996
				EP	A1	470569	12-02-1992
				EP	B1	470569	22-11-1995
				US	A	5202352	13-04-1993
JP	A2	6329542	29-11-1994			none	
US	A	5886026	23-03-1999	AT	E	154757	15-07-1997
				AU	A1	71192/94	20-02-1995
				AU	B2	693797	09-07-1998
				AU	A1	69911/98	16-07-1998
				CA	AA	2167268	02-02-1995
				CN	A	1130866	11-09-1996
				DE	C0	69403966	31-07-1997
				DE	T2	69403966	05-02-1998
				DK	T3	706376	13-10-1997
				EP	A1	706376	17-04-1996
				EP	B1	706376	25-06-1997
				EP	A2	797988	01-10-1997
				ES	T3	2106553	01-11-1997
				GR	T3	3024833	30-01-1998
				JP	T2	9503488	08-04-1997
				NO	A0	960226	18-01-1996
				NO	A	960226	18-03-1996
				NZ	A	268326	19-12-1997
				WO	A1	9503036	02-02-1995
				US	A	5716981	10-02-1998
				US	A	5994341	30-11-1999
US	A	6015541	18-01-2000	AU	A1	12705/99	24-05-1999
				AU	A1	13784/99	24-05-1999
				WO	A1	9922774	14-05-1999
				WO	A1	9922775	14-05-1999